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The Molecular Structure of Six-Membered Lactams Related to the Lactam Rule[1]

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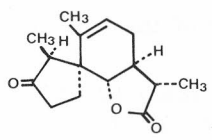
Stereochemistry of isodihydrolumisantoninlactam (*2*) was determined by means of X-ray analysis and CD. The six-membered lactam ring of *2* and D-glucono-1,5-lactam (*3*) is in halfchair conformation in agreement with the lactam rule.

INTRODUCTION

Some time ago, we proposed the lactam rule[3] for correlation of the n—π* Cotton effect with the conformation of a seven-membered lactam ring and the classification of solely two types A (+ve) and B (—ve).[2] This rule should be applicable to four-membered, five-membered, and six-membered lactam rings too, owing to the coplanarity of the lactam (C—NH—CO—C) moiety.[4]



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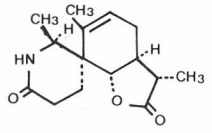

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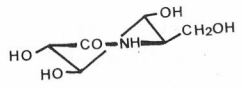

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For the confirmation of the lactam rule we carried out X-ray analyses of some lactams.[2,5,6] We herewith wish to report the stereochemistry of a six-membered lactam by means of X-ray analysis and CD data of isodihydrolumisantoninlactam *(2)* prepared from isodihydrolumisantonin *(1)*,[7] and D-glucono-1,5-lactam *(3)*.[8]

EXPERIMENTAL

Preparation of Isodihydrolumisantoninlactam [(1S,2S,6R,7S,2'S-8-Aza-5,7-dimethyl-9-oxo-spiro[5,5]-4-undecen-2-(1'-methylethan)-1-olide; 2]

A mixture of isodihydrolumisantonin[7] (*1*; 340 mg), sodium azide (200 mg), and conc. sulfuric acid (1.5 ml) in chloroform (10 ml) was stirred for 30 minutes at —10 °C. After stirring for 3 hours at room temperature, the reaction mixture was left overnight. The excess of conc. sulfuric acid was neutralized with 5% $NaHCO_3$ and the aqueous solution was extracted with chloroform. After removal of the

solvent, the residue was crystallized from methanol to give the lactam (*2*; 256 mg) as colorless plates, *m. p.* > 300 °C. IR^{KBr} cm^{-1}: 3400 (NH), 1767 (lactone), 1670, 1644 (lactam). CD (MeOH) $[\Theta]^{25}$ (nm): +1282 (229.2).

Anal. Calcd. for $C_{15}H_{21}O_3N$: C 68.41; H 8.03; N 5.31. Found: C 68.59; H 7.70; N 5.12.

X-Ray Analysis of the Lactam (2)

A crystal of the dimensions of 0.2 × 0.3 × 0.2 mm^3 was used for intensity measurements. Three-dimensional intensity data were collected on a Rigaku automatic four-circle diffractometer (AFC-4) with graphite monochromated Cu$K\alpha$ radiation. A total of 1039 independent reflections with $|F_o| > 3\sigma|F_o|$ were collected up to 2Θ of 140° and corrected for Lorentz and polarization factors but not for the absorption.

Crystal Data

$C_{15}H_{21}O_3N$, *MW* 263.33, *m. p.* > 300 °C, crystal system: monoclinic, space group: $P2_1$, $a = 10.203(2)$, $b = 7.417(1)$, $c = 9.021(2)$ Å, $\beta = 91.82(1)°$, $V = 682.3$ Å^3, $Z = 2$, $D_c = 1.282$ g cm^{-3}.

Determination and Refinement of the Structure

The crystal structure was solved by the multi-solution method (MULTAN).[9] The E-map showed positions and bond relations for all the non-hydrogen atoms. Refinement of positional parameters of the nineteen atoms was carried out by the block-diagonal least-squares method, the quantity minimized being $\Sigma w(|F_o| - |F_c|)^2$, with $w = 1.0$ for all the reflections used. All the hydrogen atoms of the molecule were found from the difference map. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms with isotropic thermal parameters. Refinement by the block-diagonal least-squares method gave the final R value of 0.004 for 920 reflections. The atomic scattering factors for C, O, N were given by Cromer and Mann,[10] and that for H by Stewart *et al.*[11] The atomic coordinates and their equivalent isotropic temperature factors are listed in Table I.[12]

RESULTS AND DISCUSSION

A perspective drawing of the molecular structure of the lactam is shown in Figure 1 with atomic numbering.

The bond angles and bond length are listed in Table IV. As shown in Table IV, the conformation of the lactam ring is the half-chair form which is similar to that of D-glucono-1,5-lactam.[5] The torsional angle of the lactam ring (C12—N1—C11—C10) is 10(2)°, which has confirmed that the lactam group of the six-membered ring is also nearly planar.

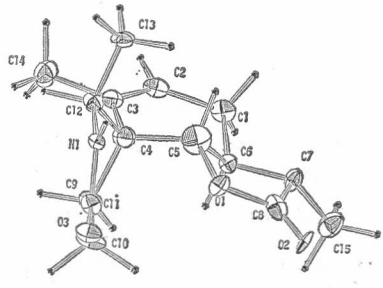

Figure 1. A perspective view of the lactam (*2*) molecule and atomic numbering.

TABLE I

Atomic coordinates (× 10^4) and equivalent isotropic temperature factors (Standard deviations in parentheses)

Atom	x	y	z	B_{eq}/Å^2 [a]
O 1	8861(7)	4454(13)	9198(7)	2.4
O 2	10378(9)	4042(18)	10985(9)	2.1
O 3	5435(8)	3450(13)	10528(9)	3.0
N 1	5941(9)	5100(16)	8546(11)	1.4
C 1	10404(11)	4445(21)	5572(13)	2.9
C 2	9162(11)	4353(18)	4604(12)	2.6
C 3	7932(12)	4172(19)	5100(12)	2.7
C 4	7588(9)	4111(16)	6765(11)	3.0
C 5	8835(10)	4816(18)	7601(11)	5.0
C 6	10090(10)	3791(17)	7127(12)	2.0
C 7	11039(10)	4310(20)	8406(12)	2.4
C 8	10123(12)	4252(20)	9718(15)	3.2
C 9	7176(12)	2132(18)	7143(14)	2.6
C10	6635(14)	1897(18)	8709(15)	3.1
C11	5960(11)	3503(19)	9286(12)	2.3
C12	6393(11)	5343(17)	7024(13)	2.4
C13	6655(12)	7356(17)	6801(15)	2.8
C14	6809(14)	4033(25)	3951(14)	4.2
C15	12233(13)	3058(24)	8598(16)	3.9

[a] W. C. Hamilton, *Acta Crystallogr.* **12** (1959) 609.

TABLE II

Bond lengths (Å) (Standard deviations in parentheses)

O 1—C 5 = 1.46(1)	C 3—C14 = 1.52(2)
O 1—C 8 = 1.36(1)	C 4—C 5 = 1.55(1)
O 2—C 8 = 1.17(2)	C 4—C 9 = 1.57(2)
O 3—C11 = 1.26(1)	C 4—C12 = 1.55(2)
N 1—C11 = 1.36(2)	C 5—C 6 = 1.56(2)
N 1—C12 = 1.47(2)	C 6—C 7 = 1.53(1)
C 1—C 2 = 1.52(2)	C 7—C 8 = 1.53(2)
C 1—C 6 = 1.53(2)	C 7—C15 = 1.54(2)
C 2—C 3 = 1.35(2)	C 9—C10 = 1.54(2)
C 3—C 4 = 1.55(2)	C10—C11 = 1.48(2)
	C12—C13 = 1.53(2)
N 1—H(N1) = 1.07(13)	C12—H12 = 1.10(8)
C 1—H 1 = 1.05(14)	C13—H13 = 1.09(13)
C 1—H 1′ = 1.11(14)	C13—H13′ = 1.10(13)
C 2—H 2 = 1.08(8)	C13—H13″ = 1.06(12)
C 5—H 5 = 1.11(10)	C14—H14 = 1.09(12)
C 6—H 6 = 1.08(9)	C14—H14′ = 1.09(14)
C 9—H 9 = 1.09(13)	C14—H14″ = 1.11(14)
C 9—H 9′ = 1.12(13)	C15—H16 = 1.08(12)
C10—H10 = 1.11(12)	C15—H16′ = 1.09(15)
C10—H10′ = 1.08(13)	C15—H16″ = 1.09(12)

TABLE III

Bond angles (°) (Standard deviations in parentheses)

C 5—O 1—C 8	= 110.2(9)	C 1—C 6—C 7	= 117.8(10)
C11—N 1—C12	= 124.3(10)	C 5—C 6—C 7	= 100.1(9)
C 2—C 1—C 6	= 108.6(9)	C 6—C 7—C 8	= 100.9(9)
C 1—C 2—C 3	= 125.5(10)	C 6—C 7—C15	= 114.4(11)
C 2—C 3—C 4	= 124.3(10)	C 8—C 7—C15	= 113.4(11)
C 4—C 3—C14	= 117.8(10)	O 1—C 8—O 2	= 121.8(16)
C 3—C 4—C 5	= 104.6(8)	O 1—C 8—C 7	= 108.9(10)
C 3—C 4—C 9	= 108.1(10)	O 2—C 8—C 7	= 129.3(11)
C 3—C 4—C12	= 109.3(9)	C 4—C 9—C10	= 114.3(10)
C 5—C 4—C 9	= 115.6(9)	C 9—C10—C11	= 114.6(11)
C 5—C 4—C12	= 111.5(10)	O 3—C11—N 1	= 119.1(12)
C 9—C 4—C12	= 107.6(9)	O 3—C11—C10	= 118.9(12)
O 1—C 5—C 4	= 113.9(9)	N 1—C11—C10	= 121.9(10)
O 1—C 5—C 6	= 101.0(8)	N 1—C12—C 4	= 109.9) 9)
C 4—C 5—C 6	= 111.7(9)	N 1—C12—C13	= 107.5(10)
C 1—C 6—C 5	= 107.1(9)	C 4—C12—C13	= 114.9(10)
C11—N 1—H(N1)	= 112.2(71)	C11—C10—H10′	= 108.1(70)
C12—N 1—H(N1)	= 123.4(71)	H10—C10—H10′	= 108.2(100)
C 2—C 1—H 1	= 111.9(68)	N 1—C12—H12	= 109.3(44)
C 2—C 1—H 1′	= 108.1(64)	C 4—C12—H12	= 110.7(47)
C 6—C 1—H 1	= 111.1(68)	C13—C12—H12	= 104.4(50)
C 6—C 1—H 1′	= 107.4(70)	C12—C13—H13	= 109.0(75)
H 1—C 1—H 1′	= 109.6(103)	C12—C13—H13′	= 108.2(77)
C 1—C 2—H 2	= 119.9(41)	C12—C13—H13″	= 108.9(77)
C 3—C 2—H 2	= 114.6(41)	H13—C13—H13′	= 108.8(94)
C 2—C 3—C14	= 117.8(10)	H13—C13—H13″	= 110.8(94)
O 1—C 5—H 5	= 111.1(44)	H13′—C13—H13″	= 111.1(98)
C 4—C 5—H 5	= 110.3(43)	C 3—C14—H14	= 111.0(62)
C 6—C 5—H 5	= 108.3(44)	C 3—C14—H14′	= 111.3(69)
C 1—C 6—H 6	= 111.2(45)	C 3—C14—H14″	= 109.4(66)
C 5—C 6—H 6	= 110.6(44)	H14—C14—H14′	= 108.8(102)
C 7—C 6—H 6	= 109.5(44)	H14—C14—H14″	= 108.0(103)
C 4—C 9—H 9	= 110.1(73)	H14′—C14—H14″	= 108.3(101)
C 4—C 9—H 9′	= 109.2(77)	C 7—C15—H16	= 111.3(77)
C10—C 9—H 9	= 108.8(67)	C 7—C15—H16′	= 109.1(69)
C10—C 9—H 9′	= 107.5(67)	C 7—C15—H16″	= 110.5(70)
H 9—C 9—H 9′	= 107.2(100)	H16—C15—H16′	= 109.1(102)
C 9—C10—H10	= 108.7(65)	H16—C15—H16″	= 109.0(91)
C 9—C10—H10′	= 110.5(68)	H16′—C15—H16″	= 107.9(104)
C11—C10—H10	= 106.5(72)		

TABLE IV

Some torsional angles (°) (Standard deviations in parentheses)

C12—N1 —C11—C10 =	10(2)
N1 —C11—C10—C9 =	—6(2)
C11—C10—C9 —C4 =	30(2)
C10—C9 —C4 —C12 =	—55(1)
C9 —C4 —C12—N1 =	55(1)
C4 —C12—N1 —C11 =	—36(2)

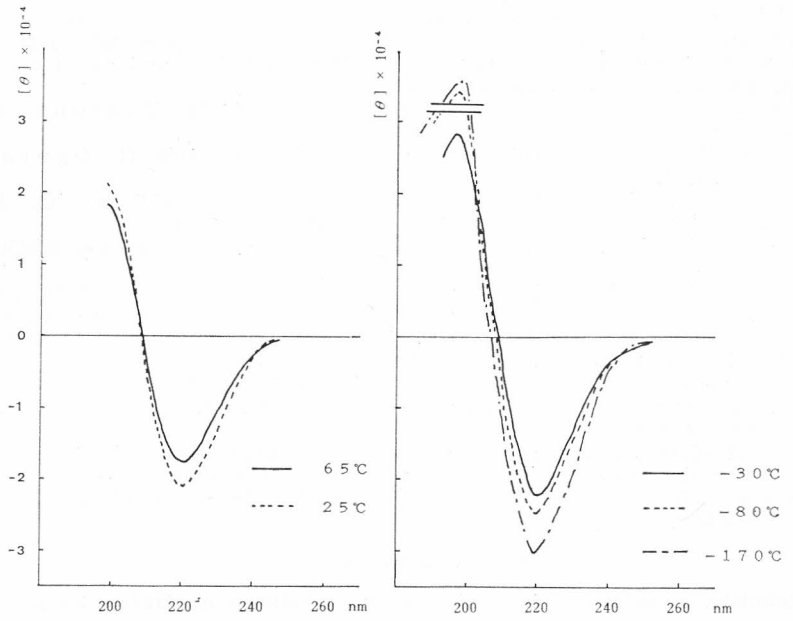

Figure 2. CD curves of D-glucono-1,5-lactam (*3*) (Ether : EtOH : MeOH = 20 : 1 : 1).

Figure 3. Projection of six-membered lactam rings (A) and (B).

As shown in Figure 2, CD curves of D-glucono-1,5-lactam[8] (*3*, conformation B) show a negative n—π* Cotton effect both at higher (65 °C) and at lower temperatures (—30, —80, —170 °C). On the other hand, it was noted with interest that a positive n—π* Cotton effect $[\Theta]_{229.2}$ + 1282 was found for the lactam (*2*, conformation A).

These results prove that Ogura's lactam rule could be also applied to six-membered lactam rings A (+ve) and B (—ve), as shown in Figure 3.

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12. Tables of observed and calculated structure factors, isotropic thermal parameters and the atomic coordinates of hydrogen atoms and anisotropic thermal parameters of non-hydrogen atoms are available from one of the authors (H. T.) on request.

SAŽETAK

Molekulska struktura šestočlanih laktama u odnosu na laktamsko pravilo

Hiroaki Takayanagi i Haruo Ogura

Stereokemija izohidrolumizantonin-laktama *(2)* određena je rentgenskom strukturnom analizom i iz CD krivulja. Šestočlani laktamski prsten spoja *2* i D-glukono-1,5-laktama *(3)* nalazi se u konformaciji polu-stolca, što je u skladu s laktamskim pravilom.